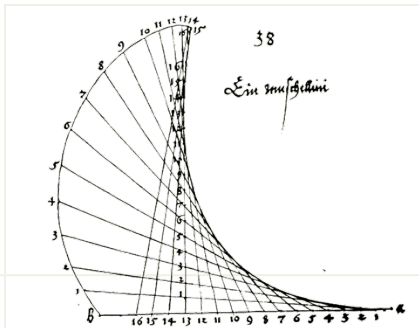


PARAMETER SENSITIVITY ANALYSIS OF A TWO-DIMENSIONAL SKIN DIFFUSION MODEL

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Goethe Center for Scientific Computing
Johann Wolfgang Goethe University
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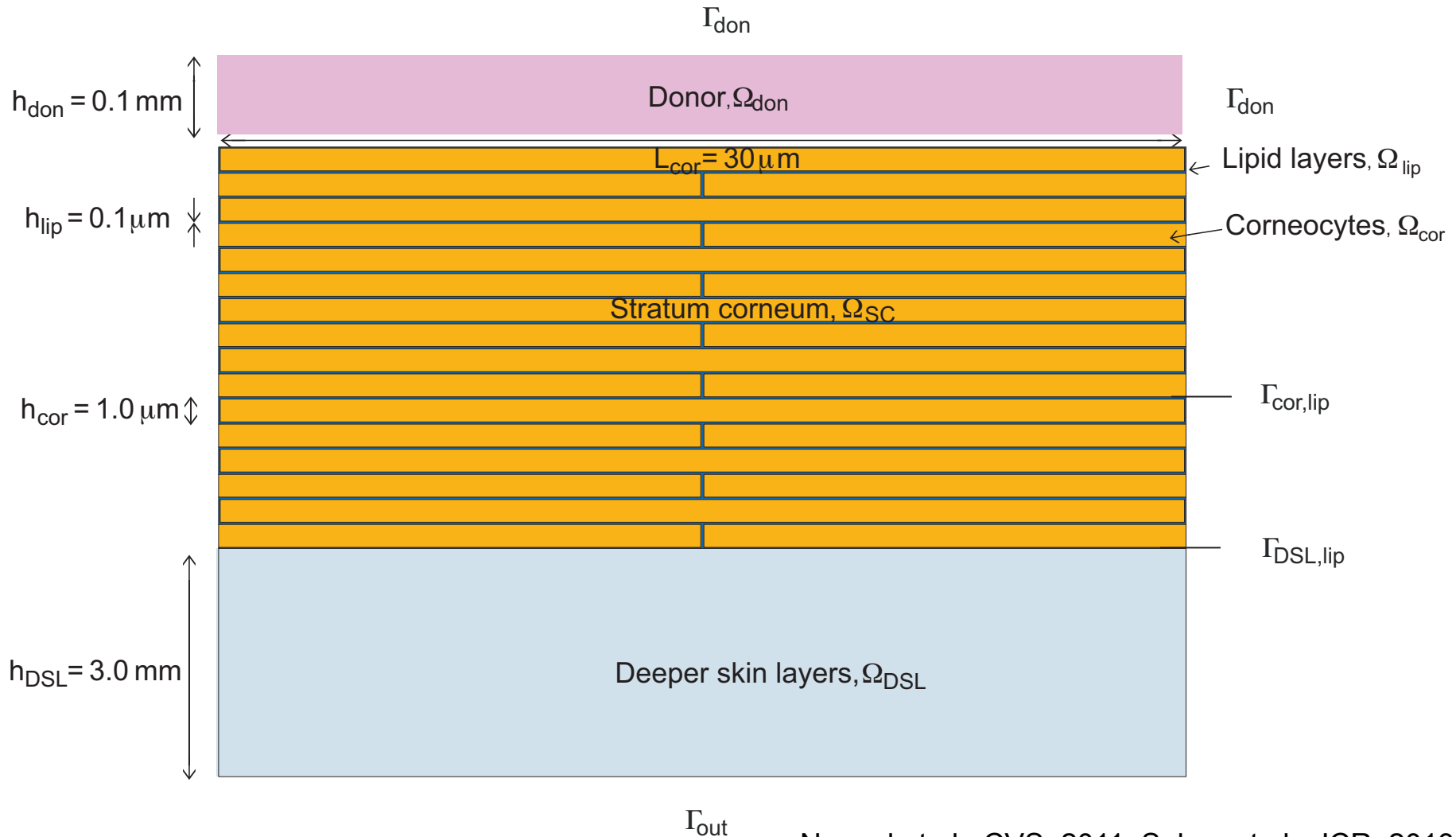
IMG 2016, December 9, 2016

Outline

- **2-D MICRO diffusion model for skin penetration after finite dosing**
- **Mass profiles over time (donor, SC, deeper skin layers, acceptor)**
- **Influence of different values of diffusion and partition coefficients on transient skin penetration**
- **Time-dependent sensitivity of input parameters**
- **Identification of key parameters for predicting skin penetration**
- **Influence of skin thickness on transient skin penetration**

Model Geometry (2D)

Simulation of finite dose experiments



Model Equations

Finite dose experiments

Diffusion Equation

$$\partial_t c_i(x, t) - \nabla \cdot (D_i \nabla c_i(x, t)) = 0 \quad \text{in } \Omega_i$$

1st Transmission Condition

$$c_i = K_{i/j} c_j \quad \text{on } \Gamma_{i/j} \quad i, j \in \{don, lip, cor, dsl\}$$

2nd Transmission Condition

$$(D_i \nabla c_i + D_j \nabla c_j) \cdot \vec{n} = 0 \quad \text{on } \Gamma_{i/j}$$

Boundary Conditions

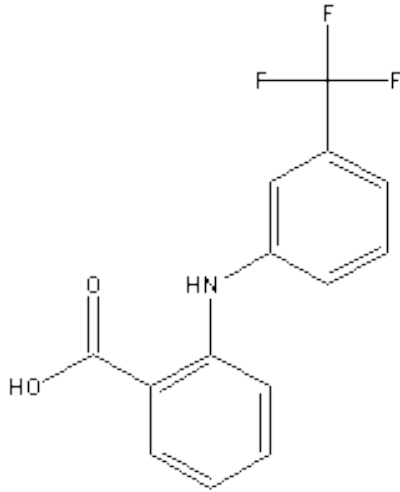
$$\frac{\partial c_i(x, y, t)}{\partial y} = 0 \quad \text{on } \Gamma_l \cup \Gamma_r \cup \Gamma_u$$

$$c_{acc}(x, \Gamma_o, t) = 0$$

Initial Conditions

$$c_{don}(x, \Gamma_u, t) = c_0, \quad c_{skin}(x, y, 0) = 0$$

Model Substances

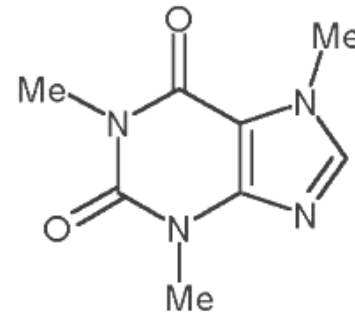


Flufenamic acid (FFA)

MW 281.23

$\log K_{\text{Oct/Wat}}$ 3.8

Lipophilic



Caffeine (CAF)

MW 194.2

$\log K_{\text{Oct/Wat}}$ - 0.13

Hydrophilic

Diffusion Model (2D)

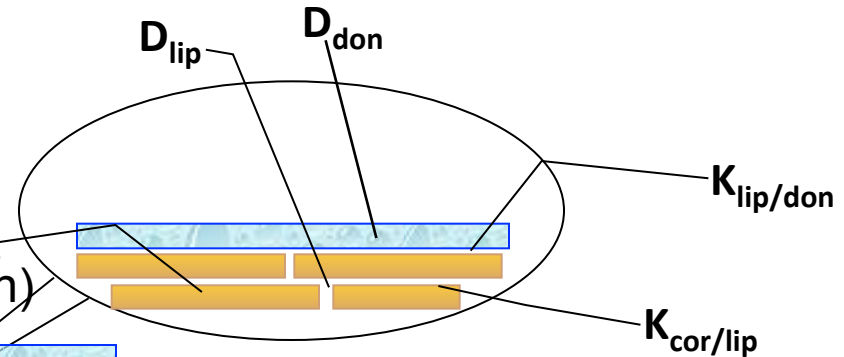
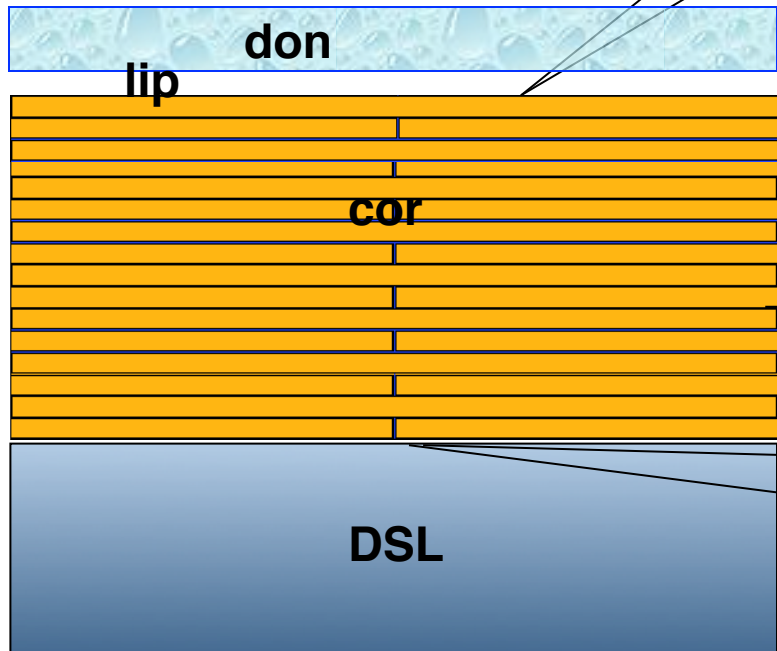
Input Parameters

Diffusion coefficients

D_{lip} , D_{SC} , D_{DSL}

D_{cor} (equiv. membrane)

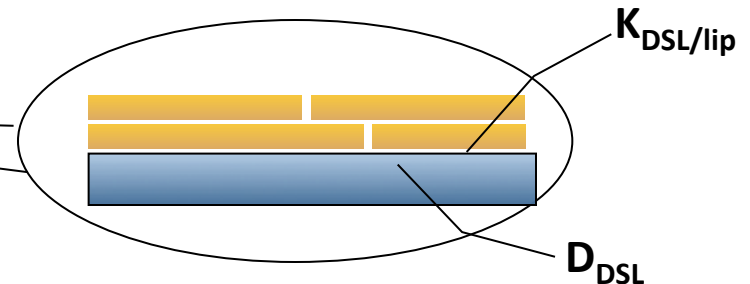
D_{don} (relationship by Anderson)



Partition coefficients

$K_{lip/don}$, $K_{SC/don}$ (equilibration)

$K_{cor/lip}$, $K_{DSL/lip}$ (indirect)



Input Parameters

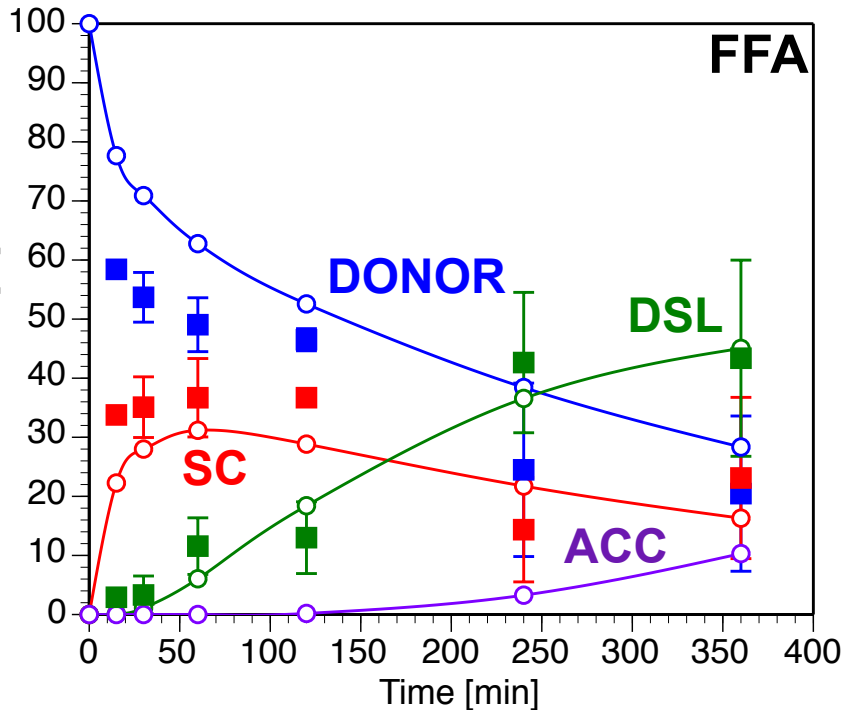
Diffusion coefficients and Partition coefficients

Parameter	Unit	FFA	CAF
D_{DON}	$[\text{cm}^2/\text{h}]$	2.47E-02	2.92E-02
D_{LIP}	$[\text{cm}^2/\text{h}]$	1.10E-04	2.10E-04
D_{COR}	$[\text{cm}^2/\text{h}]$	5.10E-07	1.70E-08
D_{DSL}	$[\text{cm}^2/\text{h}]$	4.90E-03	2.30E-03
$K_{\text{LIP/DON}}$		20.32	2.15
$K_{\text{COR/LIP}}$		0.21	2.22
$K_{\text{DSL/LIP}}$		0.1	0.08

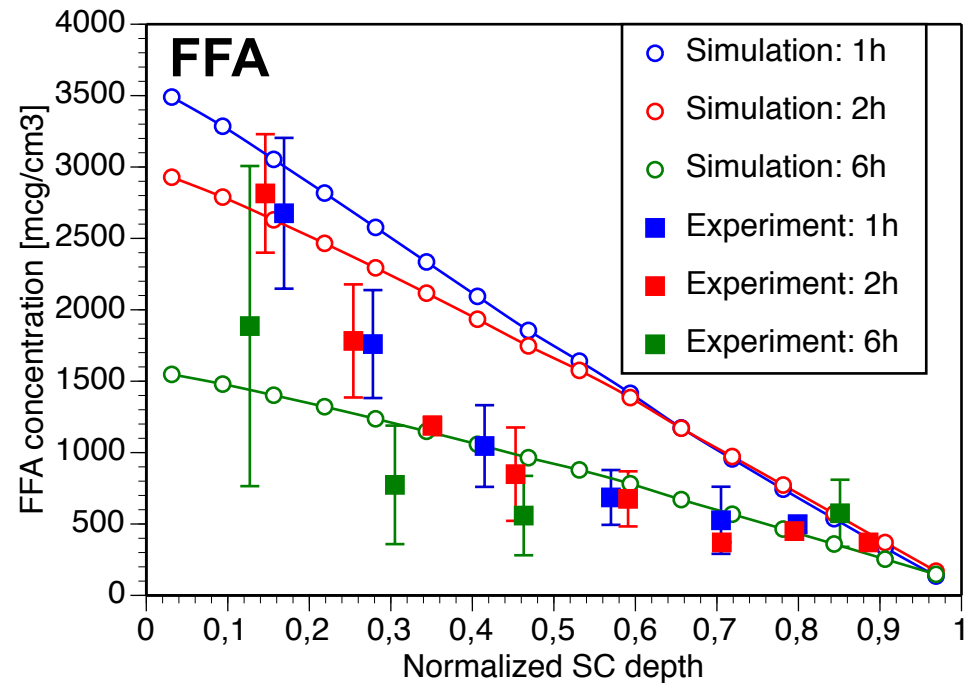
Experiment and Simulation

Mass profiles and Concentration-SC-depth profiles of FFA

Mass profiles



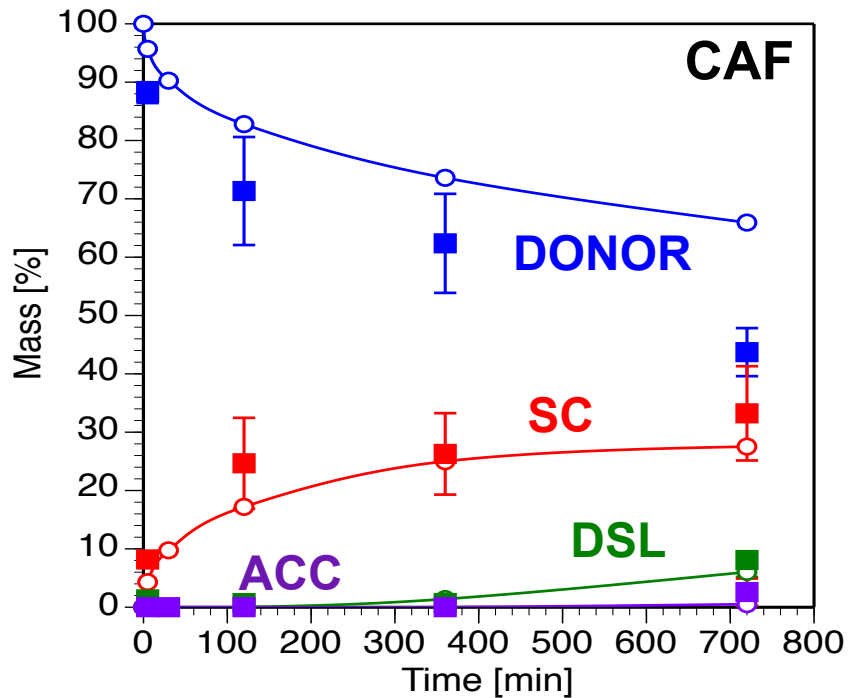
Concentration-SC-depth profiles



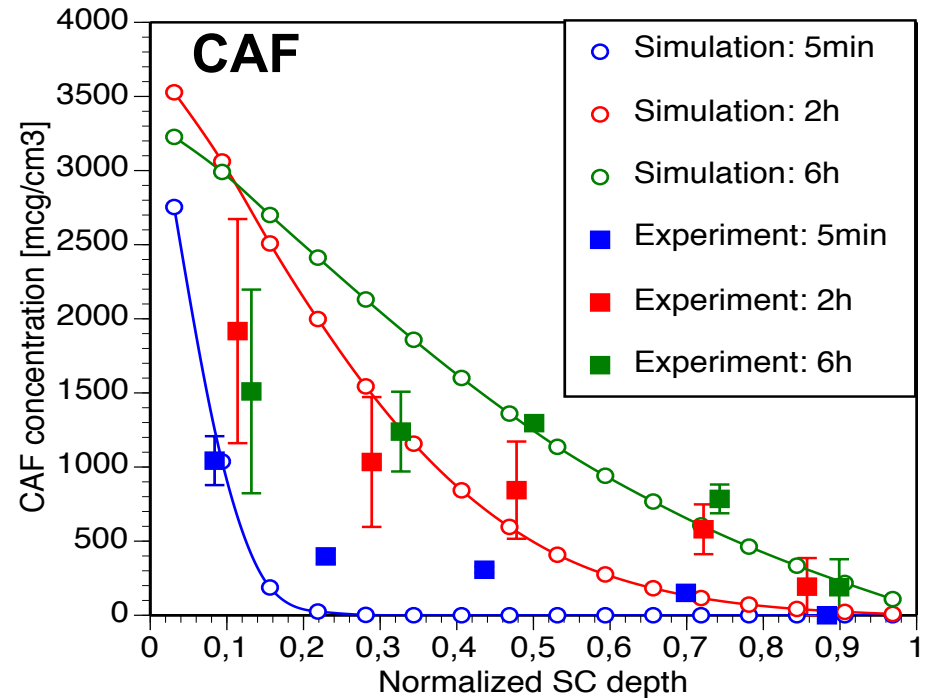
Experiment and Simulation

Mass profiles and Concentration-SC-depth profiles of CAF

Mass profiles

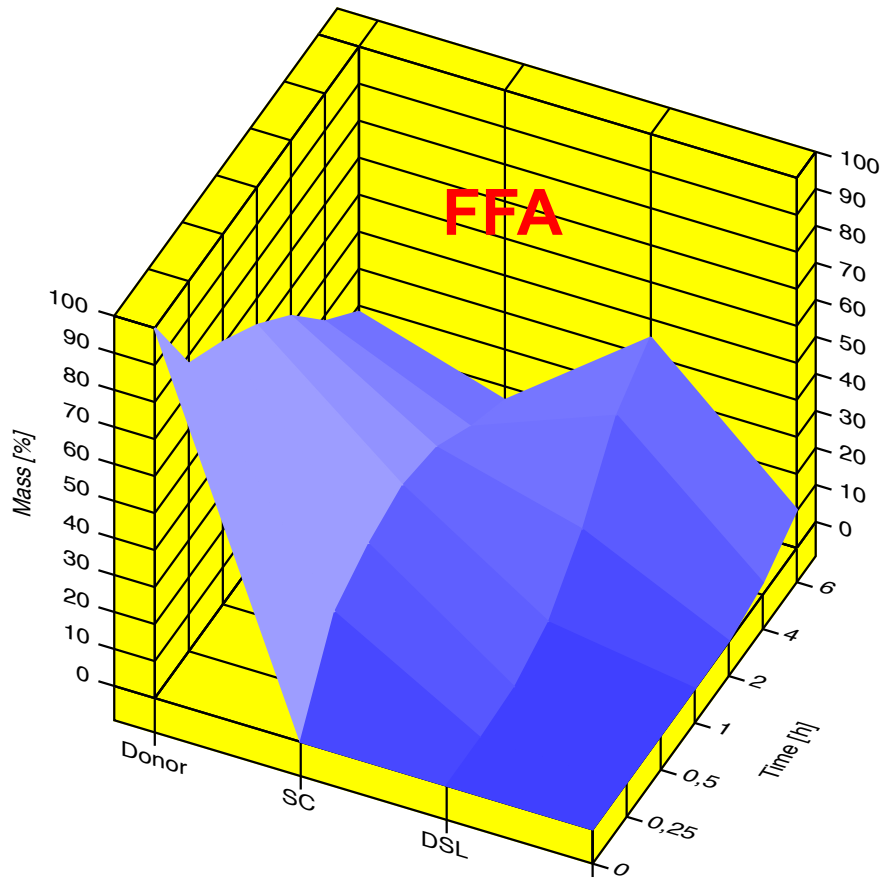


Concentration-SC-depth profiles

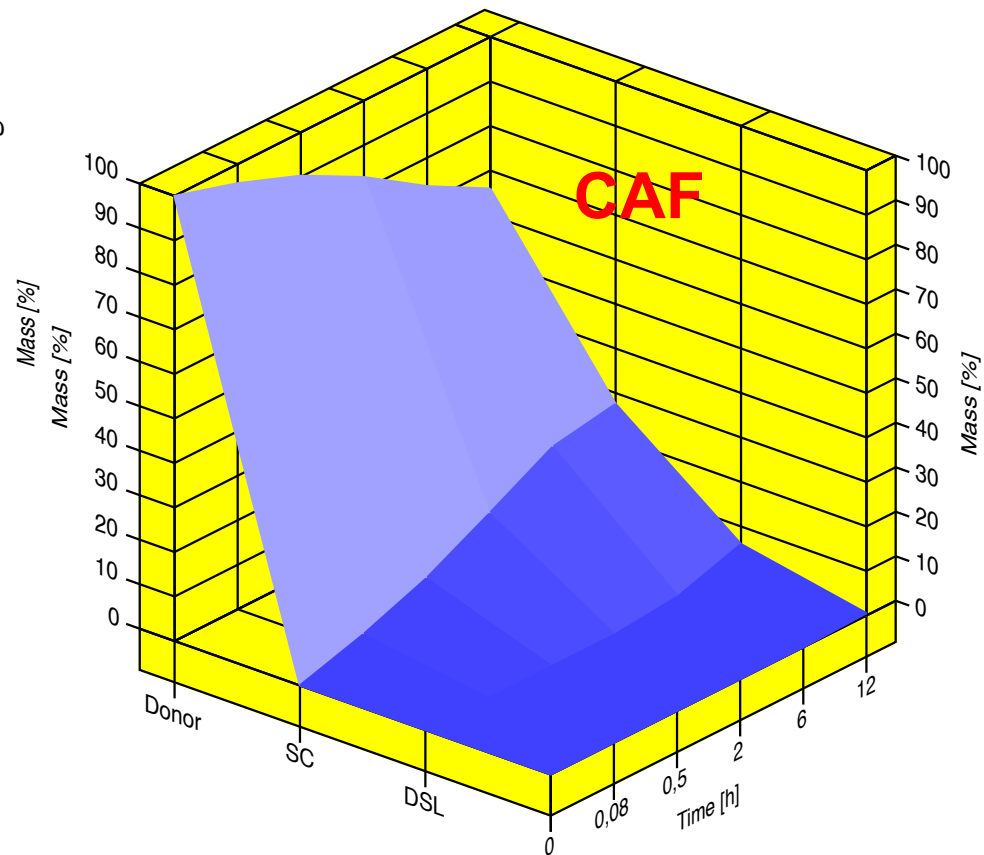


Simulation of Mass Profiles

Time-dependent mass profiles of FFA and CAF



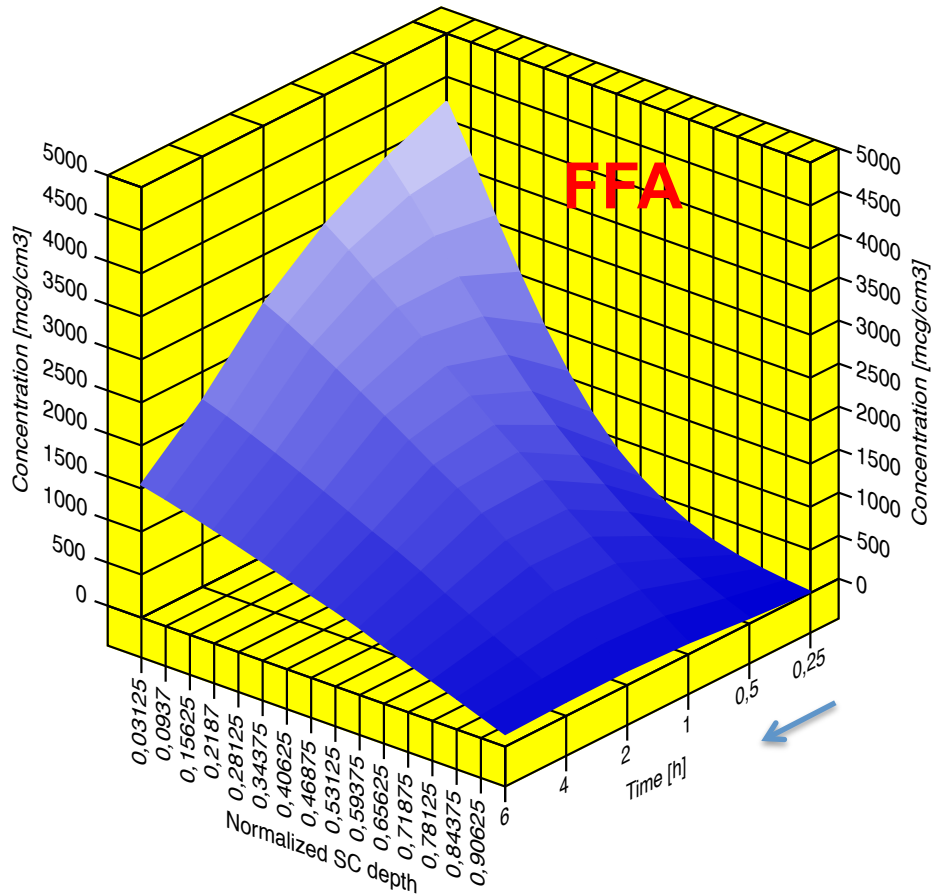
Lipophilic



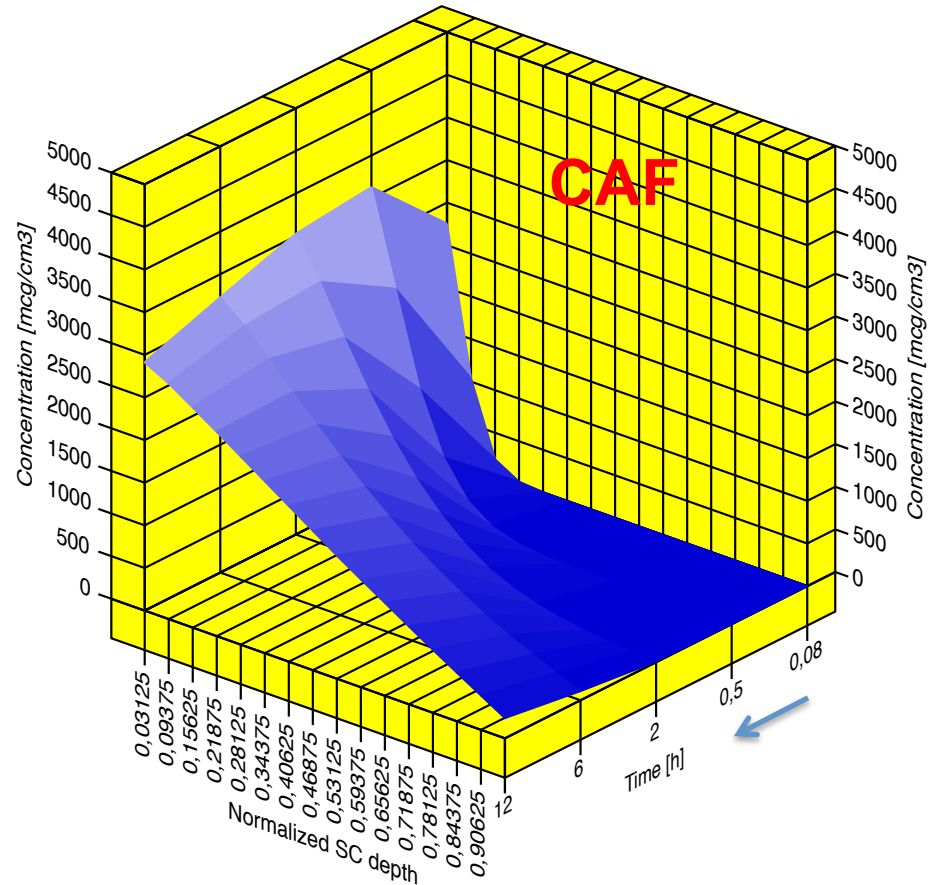
Hydrophilic

Simulation of Concentration-SC-Depth Profiles

Time-dependent concentration-SC-depth profiles of FFA and CAF



Lipophilic



Hydrophilic

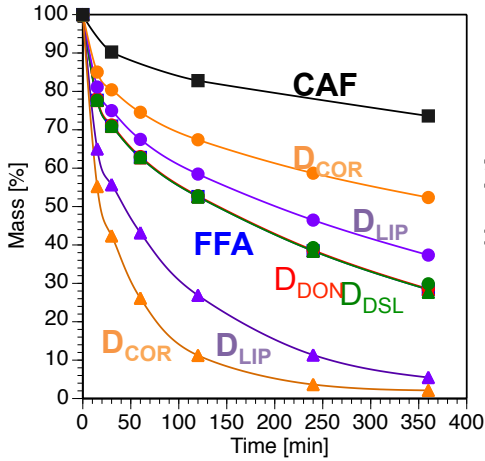
Parameter Study

Input parameter range: Diffusion coefficients and Partition coefficients

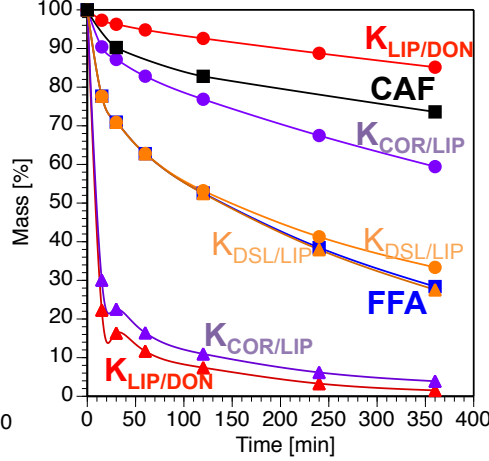
Parameter	Unit	FFA	CAF
Range D_{DON}	[cm ² /h]	2.47E-03 - 2.47E-01	2.92E-03 - 2.92E-01
Range D_{LIP}	[cm ² /h]	1.10E-05 - 1.10E-03	2.10E-05 - 2.10E-03
Range D_{COR}	[cm ² /h]	5.10E-08 - 5.10E-06	1.70E-09 - 1.70E-07
Range D_{DSL}	[cm ² /h]	4.90E-04 - 4.90E-02	2.30E-04 - 2.30E-02
Range $K_{\text{LIP/DON}}$		2.032 – 203.2	0.215 – 21.5
Range $K_{\text{COR/LIP}}$		0.021 – 2.1	0.222 – 22.2
Range $K_{\text{DSL/LIP}}$		0.01 – 1.0	0.008 – 0.8

Parameter Study on FFA Mass Profiles

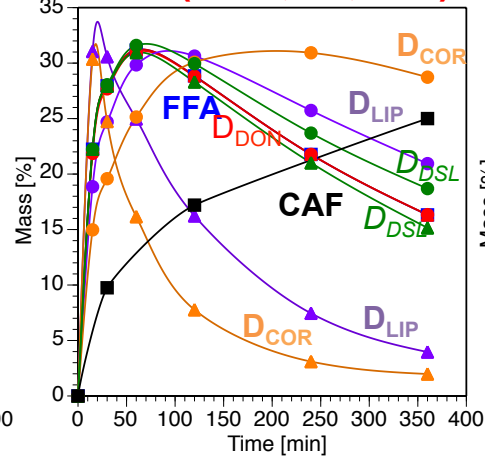
DON (0.1D,1D,10D)



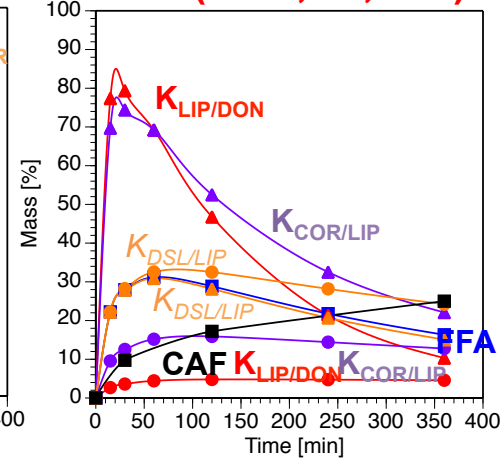
DON (0.1K,1K,10K)



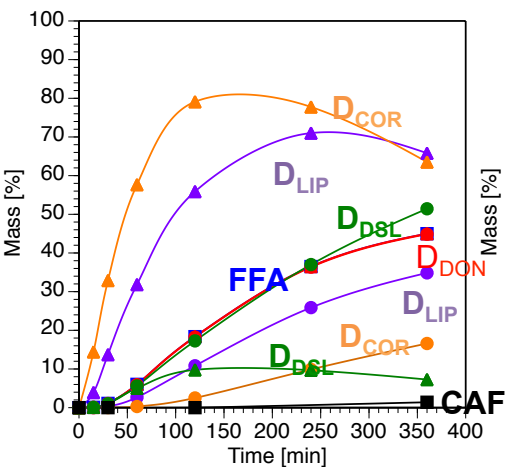
SC (0.1D,1D,10D)



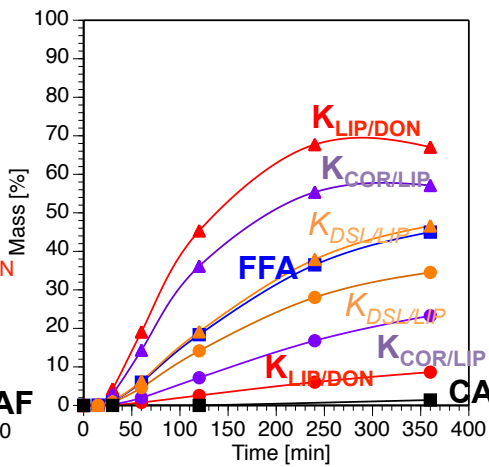
SC (0.1K,1K,10K)



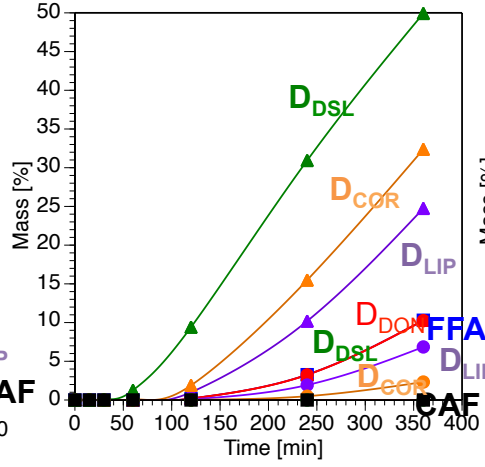
DSL (0.1D,1D,10D)



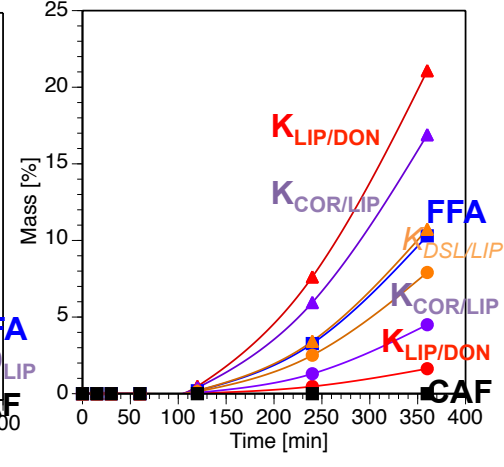
DSL (0.1K,1K,10K)



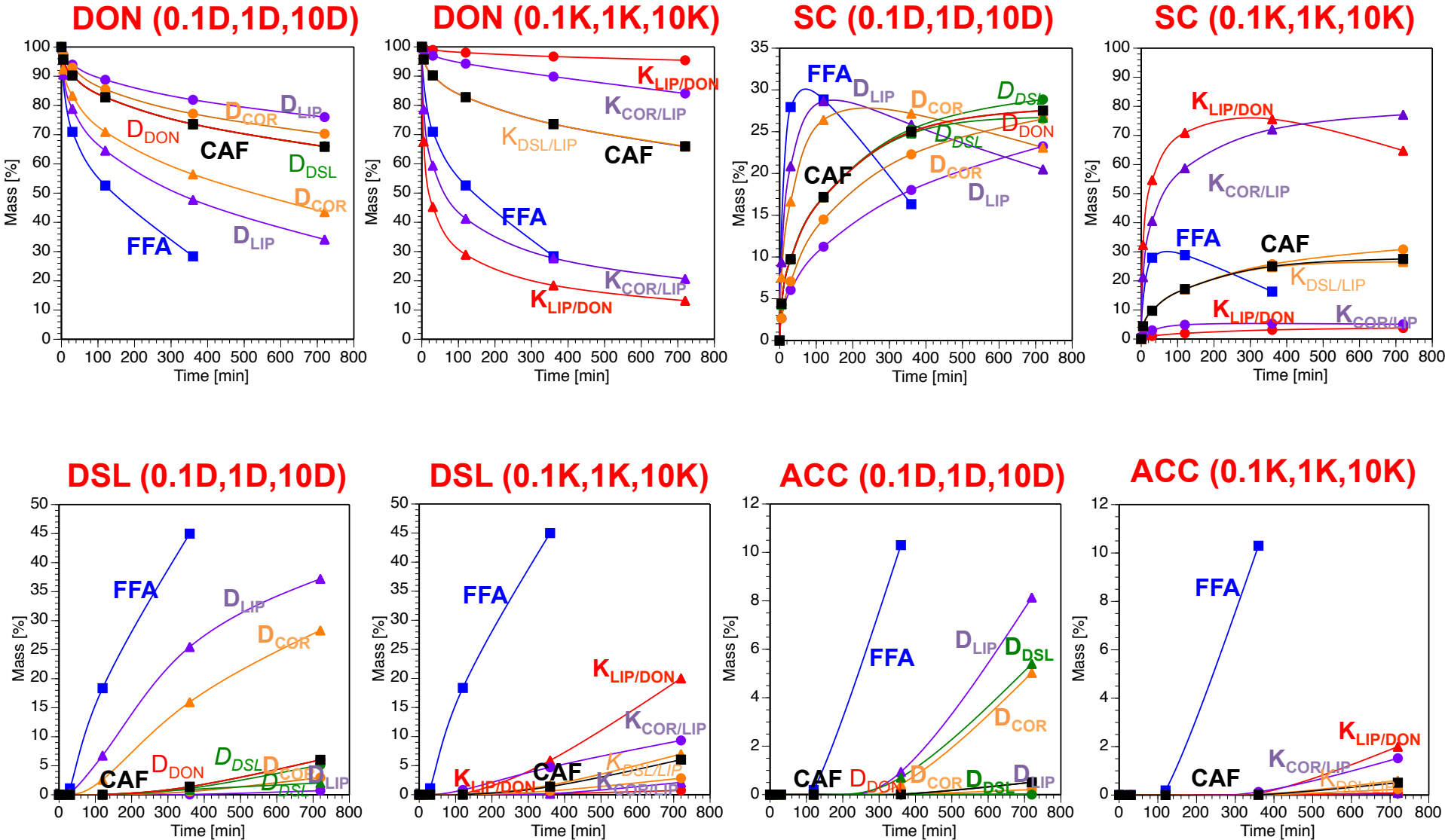
ACC (0.1D,1D,10D)



ACC (0.1K,1K,10K)



Parameter Study on CAF Mass Profiles



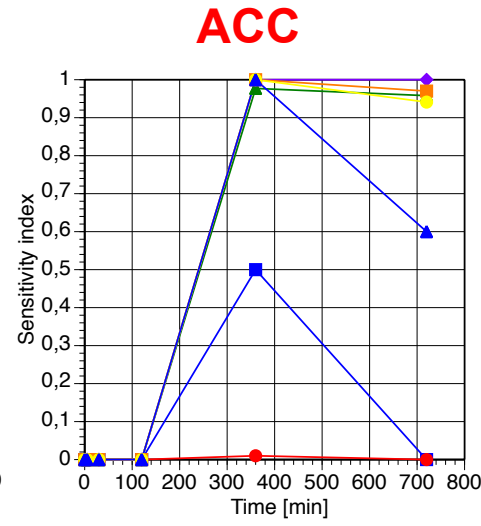
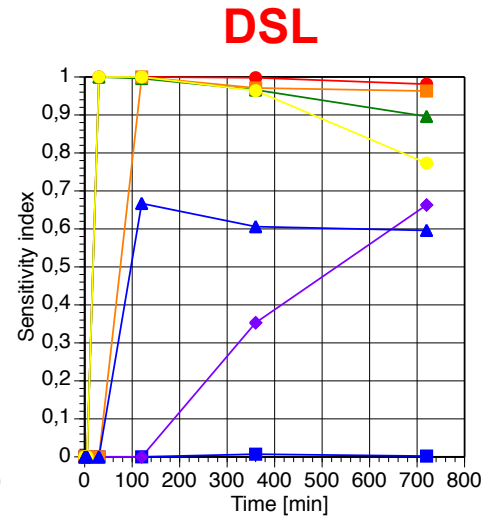
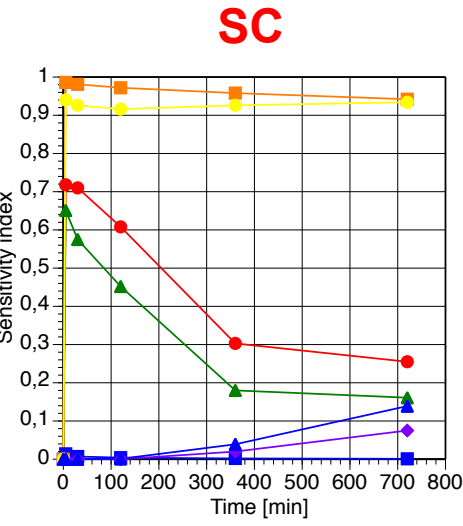
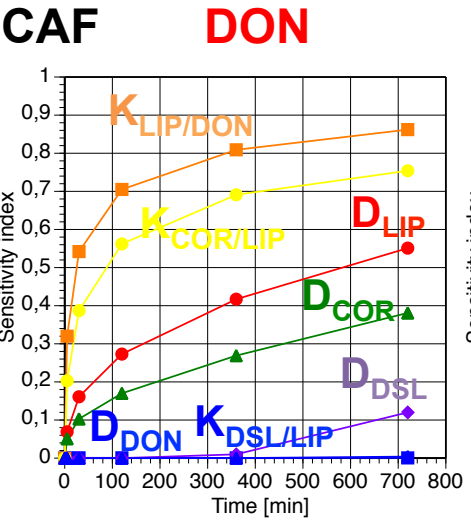
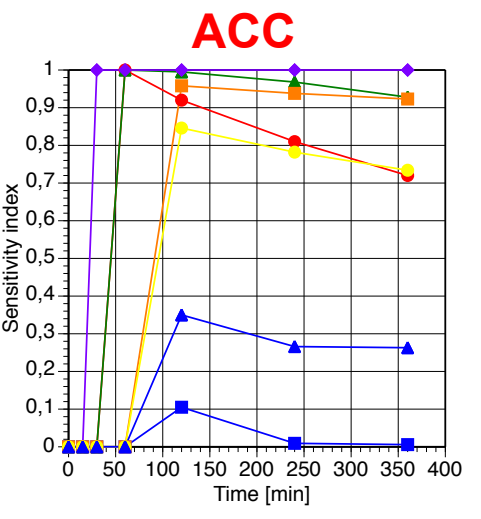
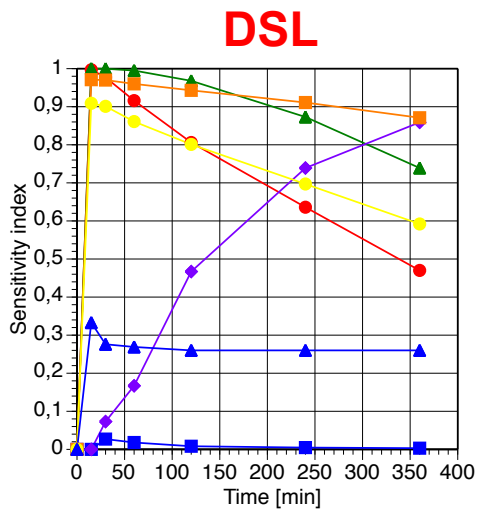
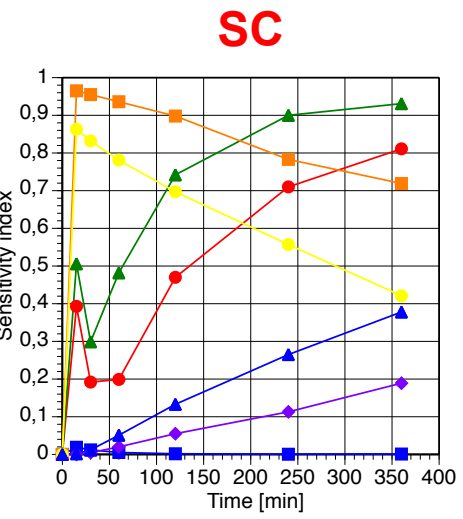
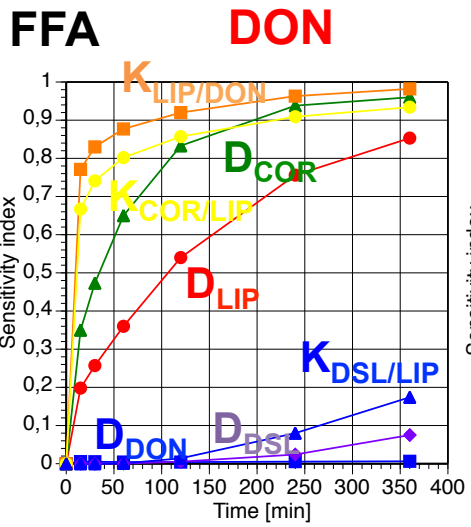
Sensitivity Index

A sensitivity index (SI) is a number calculated by a defined procedure which gives information about the relative sensitivity of results to different parameters of the model. A simple sensitivity index performed very well was proposed by Hoffman and Gardner (1983):

$$SI = (D_{\max} - D_{\min}) / D_{\max}$$

where D_{\max} is the output result when the parameter in question is set at its maximum value and D_{\min} is the result for the minimum parameter value.

Sensitivity of D and K to Mass % of FFA and CAF



Sensitivity Ranking List

FFA

Parameter	DON	SC	DSL	ACC		Sum	Score
$K_{LIP/DON}$	5.343	5.256	5.626	2.819		19.044	1
D_{COR}	4.204	3.86	5.5747	3.891		17.530	2
$K_{COR/LIP}$	4.91	4.151	4.761	2.362		16.184	3
D_{LIP}	2.964	2.775	4.802	3.45		13.991	4
D_{DSL}	0.1046	0.3816	2.305	5.0		7.791	5
$K_{DSL/LIP}$	0.2688	0.8408	1.658	0.879		3.6466	6
D_{DON}	0.0307	0.0393	0.061	0.12		0.251	7

CAF

Parameter	DON	SC	DSL	ACC		Sum	Score
$K_{LIP/DON}$	3.238	4.839	2.934	1.97		12.981	1
$K_{COR/LIP}$	2.597	4.642	3.737	1.941		12.917	2
D_{COR}	0.974	2.019	3.858	1.935		8.786	3
D_{LIP}	1.471	2.594	3.979	0.01		8.054	4
$K_{DSL/LIP}$	0.0041	0.179	1.869	1.6		3.652	5
D_{DSL}	0.13	0.095	1.016	2		3.241	6
D_{DON}	0.0035	0.028	0.009	0.5		0.541	7

Results: Sensitivity Analysis

Influence of input parameters on skin penetration

Flufenamic acid (lipophilic)

Very low sensitivity to outcome: D_{DON}

Low sensitivity to outcome: $D_{DSL} > K_{DSL/LIP}$

High sensitivity to outcome: D_{LIP}

Very high sensitivity to outcome: $K_{LIP/DON} > D_{COR} > K_{COR/LIP}$

Caffeine (hydrophilic)

Very low sensitivity to outcome: D_{DON}

Low sensitivity to outcome: $K_{DSL/LIP} > D_{DSL}$

High sensitivity to outcome: D_{LIP}

Very high sensitivity to outcome: $K_{LIP/DON} > K_{COR/LIP} > D_{COR}$

Time-varying Sensitivity Indices

FFA

		FFA DONOR D				FFA K K			
Zeit (min)		FFA_D_DON	FFA_D_LIP	FFA_D_COR	FFA_D_DSL	FFA_K_LIP/D	FFA_K_COR/LIP	FFA_K_DSL/LIP	
	0	0	0	0	0	0	0	0	
DON	15	0,0054	0,198	0,35	0	0,771	0,667	0	
	30	0,0051	0,257	0,473	0	0,83	0,741	0	
	60	0,0043	0,36	0,65	0,00032	0,877	0,802	0,0008	
	120	0,0042	0,54	0,833	0,0053	0,92	0,857	0,014	
	240	0,0054	0,756	0,938	0,024	0,963	0,909	0,08	
	360	0,0063	0,853	0,96	0,075	0,982	0,934	0,174	
		0,0307	2,964	4,204	0,1046	5,343	4,91	0,2688	
		FFA SC				FFA K_LIP/D			
Zeit (min)		FFA_D_DON	FFA_D_LIP	FFA_D_COR	FFA_D_DSL	FFA_K_LIP/D	FFA_K_COR/LIP	FFA_K_DSL/LIP	
	0	0	0	0	0	0	0	0	
SC	15	0,019	0,393	0,506	0	0,965	0,863	0,0018	
	30	0,012	0,192	0,299	0,0046	0,955	0,832	0,012	
	60	0,0051	0,199	0,482	0,02	0,936	0,781	0,051	
	120	0,0017	0,47	0,742	0,055	0,898	0,697	0,133	
	240	0,0005	0,71	0,9	0,113	0,783	0,557	0,265	
	360	0,001	0,811	0,931	0,189	0,719	0,421	0,378	
		0,0393	2,775	3,86	0,3816	5,256	4,151	0,8408	
		FFA DSL				FFA K_LIP/D			
Zeit (min)		FFA_D_DON	FFA_D_LIP	FFA_D_COR	FFA_D_DSL	FFA_K_LIP/D	FFA_K_COR/LIP	FFA_K_DSL/LIP	
	0	0	0	0	0	0	0	0	
DSL	15	0	0,997	1	0	0,971	0,909	0,333	
	30	0,027	0,977	0,9997	0,073	0,97	0,901	0,276	
	60	0,018	0,916	0,995	0,167	0,96	0,861	0,269	
	120	0,0082	0,806	0,968	0,467	0,943	0,801	0,26	
	240	0,0047	0,636	0,873	0,739	0,911	0,697	0,26	
	360	0,0031	0,47	0,739	0,859	0,871	0,592	0,26	
		0,061	4,802	5,5747	2,305	5,626	4,761	1,658	
		FFA ACC				FFA K_LIP/D			
Zeit (min)		FFA_D_DON	FFA_D_LIP	FFA_D_COR	FFA_D_DSL	FFA_K_LIP/D	FFA_K_COR/LIP	FFA_K_DSL/LIP	
	0	0	0	0	0	0	0	0	
ACC	15	0	0	0	0	0	0	0	
	30	0	0	0	1	0	0	0	
	60	0	1	1	1	0	0	0	
	120	0,105	0,92	0,995	1	0,958	0,846	0,35	
	240	0,0092	0,81	0,968	1	0,938	0,782	0,266	
	360	0,0058	0,72	0,928	1	0,923	0,734	0,263	
		0,12	3,45	3,891	5	2,819	2,362	0,879	

Time-varying Sensitivity Indices

DON

CAF DONOR	D				K			
Zeit (min)	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
0	0	0	0	0	0	0	0	0
5	0,0006	↓ 0,069	↓ 0,051	↓ 0	0,32	↓ 0,203	↓ 0	0
30	0,0008	↓ 0,161	↓ 0,103	↓ 0	0,542	↓ 0,387	↓ 0	0
120	0,0008	↑ 0,273	↓ 0,17	↓ 0	0,705	↓ 0,562	↓ 0	0
360	0,0007	↑ 0,417	↓ 0,269	↓ 0,01	0,809	↓ 0,691	↓ 0,0001	↓
720	0,0006	↑ 0,551	↓ 0,381	↓ 0,12	0,862	↓ 0,754	↓ 0,004	↓
	0,0035	1,471	0,974	0,13	3,238	2,597	0,0041	

CAF SC

CAF SC	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
Zeit (min)	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
0	0	0	0	0	0	0	0	0
5	0,014	↑ 0,718	↑ 0,651	↑ 0	0,986	↑ 0,94	↑ 0	0
30	0,007	↑ 0,71	↑ 0,575	↑ 0	0,981	↑ 0,926	↑ 0	0
120	0,004	↑ 0,608	↑ 0,452	↑ 0	0,972	↑ 0,916	↑ 0,001	↓
360	0,002	↑ 0,303	↑ 0,18	0,02	0,958	↑ 0,926	↓ 0,039	↓
720	0,001	↑ 0,255	↑ 0,161	0,075	0,942	↑ 0,934	↓ 0,139	↓
	0,028	2,594	2,019	0,095	4,839	4,642	0,179	

DSL

CAF DSL	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
Zeit (min)	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
30	0	↑ 1	↑ 1	↑ 0	0	1	↑ 0	0
120	0	↑ 1	↑ 0,996	↑ 0	1	↑ 1	↑ 0,667	↑
360	0,007	↑ 0,998	↑ 0,966	0,353	↓ 0,971	↑ 0,964	↑ 0,606	↑
720	0,002	↑ 0,981	↑ 0,896	0,663	↓ 0,963	↑ 0,773	↑ 0,596	↑
	0,009	3,979	3,858	1,016	2,934	3,737	1,869	

ACC

CAF ACC	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
Zeit (min)	CAF_D_DON	CAF_D_LIP	CAF_D_COR	CAF_D_DSL	CAF_K_LIP/DON	CAF_K_COR/LIP	CAF_K_DSL/LIP	
0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0
120	0	↓ 0	↓ 0	0	0	0	0	0
360	0,5	↓ 0,01	↓ 0,977	↑ 1	↓ 1	↑ 1	↑ 1	↑ 1
720	0	↑ 0	↑ 0,958	↑ 1	↓ 0,97	↑ 0,941	↑ 0,6	↑
	0,5	0,01	1,935	2	1,97	1,941	1,6	

Results: Time-dependent Sensitivity Analysis

Time-dependent sensitivities of input parameters

Flufenamic acid (lipophilic)

Donor: Sensitivity of all 7 parameters increases with time

SC: Sensitivity increases/decreases (3 parameters) with time

DSL: Sensitivity increases/decreases (6 parameters) with time

ACC: Sensitivity increases/decreases (6 parameters) with time

Caffeine (hydrophilic)

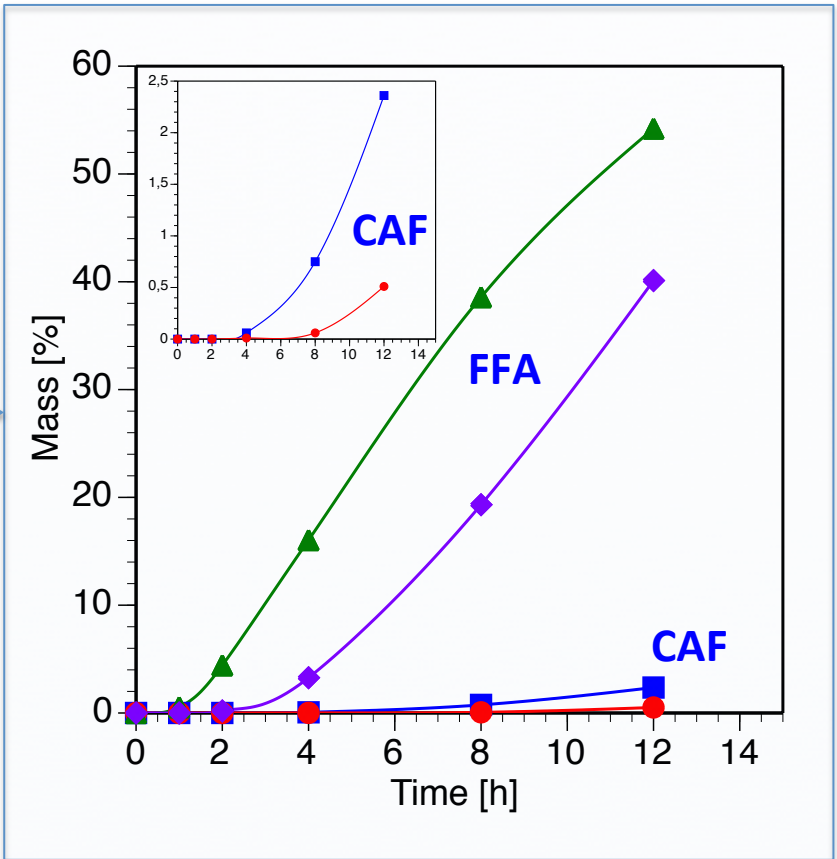
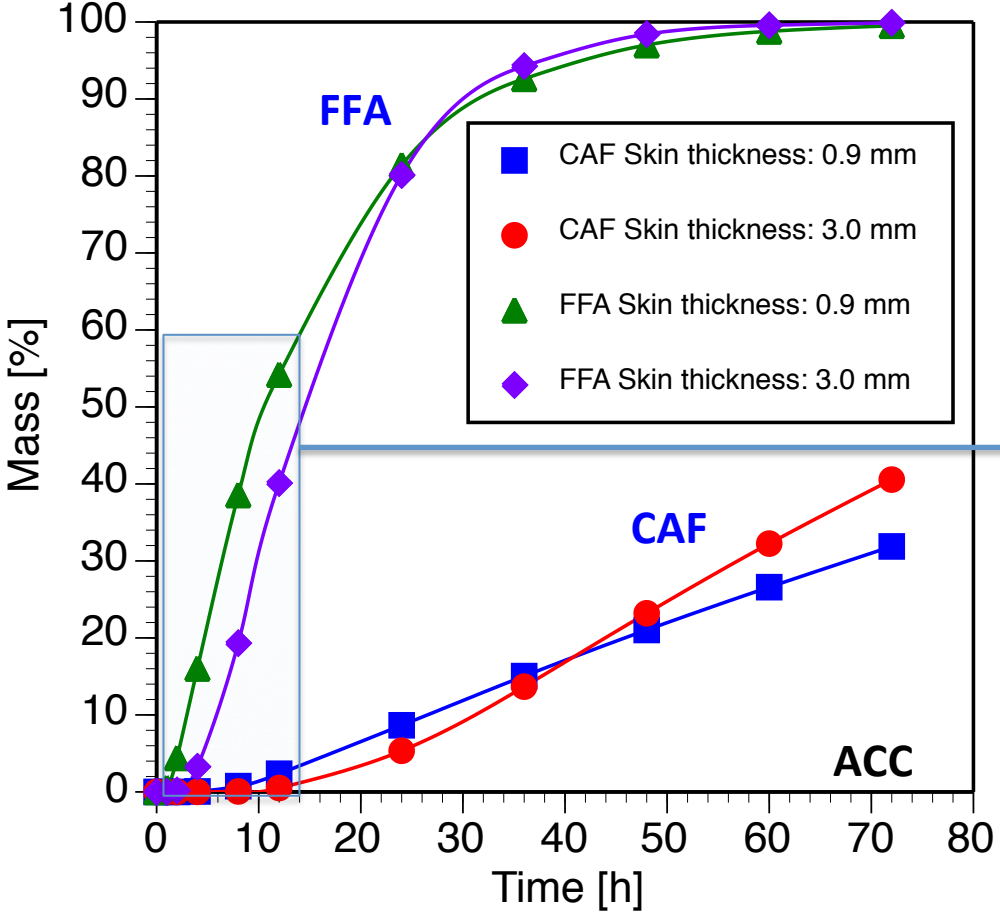
Donor: Sensitivity of all 7 parameters increases with time

SC: Sensitivity increases/decreases (5 parameters) with time

DSL: Sensitivity increases/decreases (6 parameters) with time

ACC: Sensitivity increases/decreases (6 parameters) with time

Influence of Skin Thickness on Skin Penetration



Summary

- **2-D MICRO diffusion model for skin penetration after finite dosing**
- **Mass profiles over time (donor, SC, deeper skin layers, acceptor)**
- **Influence of different values of diffusion and partition coefficients on transient skin penetration**
- **Time-dependent sensitivity of input parameters**
- **Identification of key parameters for predicting skin penetration**
- **Influence of skin thickness on transient skin penetration**

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